PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IL2009/000379	05.04.2009	09.04.2008

International Patent Classification (IPC) or both national classification and IPC
INV. A61K39/395 A61K47/48 A61P31/18 C07K16/10 C07K16/28

Applicant
TECHNION RESEARCH & DEVELOPMENT FOUNDATION LTD.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Cilensek, Zoran Telephone No. +49 89 2399-8207

Form PCT/ISA/237 (Cover Sheet) (April 2005)

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☒ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☒ on paper

      ☒ in electronic form

   c. time of filing/furnishing:

      ☒ contained in the international application as filed.

      ☒ filed together with the international application in electronic form.

      ☐ furnished subsequently to this Authority for the purposes of search.

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3,6-8,10,11,17
	No:	Claims	1,2,4,5,9,12-16
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-17
Industrial applicability (IA)	Yes:	Claims	1-17
	No:	Claims	

2. Citations and explanations

see separate sheet

Reference is made to the following documents:

D1: WO 99/49893 A (UNIV BOSTON [US]) 7 October 1999 (1999-10-07)

D2: POLAKOVA K ET AL: "Antibodies directed against the MHC-I molecule H-2Dd complexed with an antigenic peptide: similarities to a T cell receptor with the same specificity" JOURNAL OF IMMUNOLOGY, AMERICAN ASSOCIATION OF IMMUNOLOGISTS, US, vol. 165, no. 10, 1 November 2000 (2000-11-01), pages 5703-5712, XP002986050 ISSN: 0022-1767

D3: WO 91/12332 A (INST NAT SANTE RECH MED [FR]) 22 August 1991 (1991-08-22)

D4: ANIKEEVA N ET AL: "Soluble HIV-specific T cell receptor: expression, purification and analysis of the specificity" JOURNAL OF IMMUNOLOGICAL METHODS, ELSEVIER SCIENCE PUBLISHERS B.V.,AMSTERDAM, NL, vol. 277, no. 1-2, 1 June 2003 (2003-06-01), pages 75-86, XP004430548 ISSN: 0022-1759

D5: WO 2006/103429 A (AVIDEX LTD [GB]; JAKOBSEN BENT KARSTEN [GB]; LI YI [GB]; DUNN STEVEN M) 5 October 2006 (2006-10-05)

D6: US 2004/191260 A1 (REITER YORAM [IL] ET AL) 30 September 2004 (2004-09-30)

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Claims 13 (implicitly) and 15 (explicitly) relate to a subject-matter considered by this Authority to be covered by the provision of Rule 39.1(iv)/67.1(iv) PCT. The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for in a first or further medical treatment.

2 **NOVELTY** (Art. 33(2) PCT)

2.1 D1 discloses the production of antibodies specific for MHC/peptide complexes, which

are preferably attached to a cytotoxic agent, such as Pseudomonas aeruginosa exotoxin. In particular, the application teaches antibodies raised against a peptide termed 3xP17 (77-85) of HIV Gag, which is identical to SEQ ID NO:2 used in immunization in the underlying application (pages 3-5, page 15, line 22.page 21, line 16, page 23, line 6-21, pages 34-40, Table 4).

Therefore claims 1, 2, 4, 5 and 12-16 cannot be considered new in view of D1.

2.2 D2 discloses two monoclonal antibodies, KP14 and KP15, which are specific for H-2Dd complexed with an HIV envelope gp160 derived peptide known as P18-110. The antibodies bind the complex with the Kd of app. 100 nM and block the induction of CTL *in vivo* (Figures 1-8).

Therefore claims 1, 9 and 13 are not new over D2.

2.3 D3 teaches the generation of antibodies specific for MHC/peptide complexes, wherein the peptide is derived from the sequence of HIV Gag (page 1, §1-3 and page 8, § 2).

D4 discloses the production of soluble T cell receptor derived from a human CD8+ cytotoxic T lymphocyte clone D3 that recognizes the peptide SLYNTVATL (SL9), identical to SEQ ID NO:2 used in immunization in the underlying application (see the whole document).

D5 discloses the production of high affinity TCR specific for the SL9 peptide, with the Kd in the μM range (pages 27-41).

D6 discloses the use of phage display technology for the production of monoclonal antibodies specific for MHC/peptide complexes. The application suggests that the antigenic peptide may be derived from HIV-1 or HIV-2 (see the entire document, for the latter citation § 223).

2.4 Claims 3, 6-8, 10, 11 and 17 appear new in view of the cited documents. The present application does not meet the requirements of Article 33(2) PCT because the subject-matter of claims 1, 2, 4, 5, 9 and 12-16 is not new.

2.5 **INVENTIVE STEP** (Art. 33(3) PCT)

2.6 Document D1 is considered to represent the most relevant state of the art. The subject-matter of claims 3 and 10 differs in that the antibody comprises the CDRs of SEQ ID NO:3-8, encoded by SEQ ID NO:9-14.

2.7 In view of the above difference the problem to be solved may be regarded as the provision of an antibody for the MHC/SLYNTVATL complex. The solution offered in the claims cannot be considered as involving an inventive step, since the provision of such an antibody falls into a range of routine activities of the person skilled in the art. The antibody is not associated with any apparent surprising or unexpected technical effect which would merit the recognition of an inventive step.

2.8 The claims would also lack an inventive step if any of D4 or D5, disclosing the antigenic peptide of the invention, were considered as the closest prior art. The person skilled in the art would be motivated to apply the teachings of any of D2, D3 or D6 disclosing antibodies specific for MHC peptide complexes, wherein the peptides are derived from the HIV sequence, and to generate such antibodies to the SL) peptide disclosed in D4 and D5.

2.9 Claims 6-8, 11 and 17 do not appear to contain any additional features which, in combination with the features of any claim to which they refer, involve an inventive step since they encompass the modifications and uses already suggested by the prior art.

2.10 In view of the above, the present application does not meet the requirements of Article 33(3) PCT, because the subject-matter of claims 3, 6-8, 10, 11 and 17 does not involve an inventive step.

Additional remarks:

2.11 Claim 3 defines the antibody with 6 CDRs sequences, without specifying which CDR is encoded by which of the sequences. In the absence of this specification, the claim encompasses all possible combinations of the six sequences, while it is evident from the description that only one of said combinations exhibits the claimed antigen specificity and thus can be considered as a solution to the technical problem. Thus

it is considered that the claim lacks the essential technical features pertinent to the performance of the invention. Similar reasoning applies to claim 10 directed to nucleic acid sequences encoding said CDRs.

Possible steps after receipt of the international search report (ISR) and written opinion of the International Searching Authority (WO-ISA)

General information	For all international applications filed on or after 01/01/2004 the competent ISA will establish an ISR. It is accompanied by the WO-ISA. Unlike the former written opinion of the IPEA (Rule 66.2 PCT), the WO-ISA is not meant to be responded to, but to be taken into consideration for further procedural steps. This document explains about the possibilities.
Amending claims under Art. 19 PCT	Within 2 months after the date of mailing of the ISR and the WO-ISA the applicant may file amended claims under Art. 19 PCT directly with the International Bureau of WIPO. The PCT reform of 2004 did not change this procedure. For further information please see Rule 46 PCT as well as form PCT/ISA/220 and the corresponding Notes to form PCT/ISA/220.
Filing a demand for international preliminary examination	In principle, the WO-ISA will be considered as the written opinion of the IPEA. This should, in many cases, make it unnecessary to file a demand for international preliminary examination. If the applicant nevertheless wishes to file a demand this must be done before expiry of 3 months after the date of mailing of the ISR/WO-ISA or 22 months after priority date, whichever expires later (Rule 54bis PCT). Amendments under Art. 34 PCT can be filed with the IPEA as before, normally at the same time as filing the demand (Rule 66.1 (b) PCT). If a demand for international preliminary examination is filed and no comments/amendments have been received the WO-ISA will be transformed by the IPEA into an IPRP (International Preliminary Report on Patentability) which would merely reflect the content of the WO-ISA. The demand can still be withdrawn (Art. 37 PCT).
Filing informal comments	After receipt of the ISR/WO-ISA the applicant may file informal comments on the WO-ISA directly with the International Bureau of WIPO. These will be communicated to the designated Offices together with the IPRP (International Preliminary Report on Patentability) at 30 months from the priority date. Please also refer to the next box.
End of the international phase	At the end of the international phase the International Bureau of WIPO will transform the WO-ISA or, if a demand was filed, the written opinion of the IPEA into the IPRP, which will then be transmitted together with possible informal comments to the designated Offices. The IPRP replaces the former IPER (international preliminary examination report).
Relevant PCT Rules and more information	Rule 43 PCT, Rule 43bis PCT, Rule 44 PCT, Rule 44bis PCT, PCT Newsletter 12/2003, OJ 11/2003, OJ 12/2003

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